The role of gender and other factors as predictors of not receiving reperfusion therapy and of outcome in ST-segment elevation

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The Role of Gender and Other Factors as Predictors of Not Receiving Reperfusion Therapy and of Outcome in ST-Segment Elevation Myocardial Infarction

Marc Cohen MD,[1] Gian Franco Gensini MD,[2] Frans Maritz MD,[3] Enrique P. Gurfinkel MD, PhD,[4] Kurt Huber MD,[5] Ari Timerman MD, PhD,[6] Jose Santopinto MD,[7] Giancarlo Corsini MD,[8] Pierfranco Terrosu MD,[8] Florence Joulain,[9] on behalf of the TETAMI investigators

[1]Newark Beth Israel Medical Center, New Jersey, USA; [2]University of Florence, Florence, Italy; [3]Karl Bremer Hospital, Bellville, South Africa; [4]Favaloro Foundation, Buenos Aires, Argentina; [5]University Clinic for Internal Medicine, Vienna, Austria; [6]Dante Pazzanese Institute of Cardiology, São Paulo, Brazil; [7]Leonidas Lucero Municipal Hospital, Bahia Blanca, Argentina; [8]San Sebastiano Hospital, Caserta, Italy; [9]Keyrus for Aventis, Paris, France

Abstract. ***Background:*** **The standard of care for ST-segment elevation myocardial infarction (STEMI) is prompt coronary reperfusion with thrombolysis or percutaneous coronary intervention. Women have higher mortality rates than men following STEMI and fewer women are considered eligible for reperfusion therapy. We analyzed the impact of gender, and other factors, on the outcome and treatment of STEMI in the TETAMI trial and registry.**

Methods: **This exploratory analysis included 2741 patients from Treatment with Enoxaparin and Tirofiban in Acute Myocardial Infarction (TETAMI) presenting with STEMI within 24 hours of symptom onset. The primary composite end point was the combined incidence of all-cause death, recurrent myocardial infarction, and recurrent angina, at 30 days. Three multivariate analyses were performed to determine predictors of not receiving reperfusion therapy, the composite end point, or death.**

Results: **The triple end point occurred in 17.8% of women versus 13.3% of men. Reperfusion therapy was utilized in 38.2% of women versus 47.3% in men. However, age >75 years, delayed presentation, high systolic blood pressure (>100) and region (South Africa), were significant, independent predictors of not receiving reperfusion therapy. Significant predictors of the triple end point included not receiving reperfusion therapy, age >60 years, and higher Killip class. Predictors of death included age >60 years, low systolic blood pressure, higher Killip class, high heart rate, delayed presentation, and region (South Africa and South America).**

Conclusion: **Female gender was not an independent predictor of outcome or underutilization of reperfusion therapy. Factors more common in female STEMI patients (advanced age and delayed presentation) were associated with not receiving reperfusion therapy and adverse outcome. Increased awareness is needed to reduce delayed presentation after symptom onset, especially among women.**

Abbreviated abstract. **In this analysis of 2741 ST-segment elevation myocardial infarction patients in the TETAMI trial and registry, a trend was observed for women being less likely to receive reperfusion therapy and more likely to have an adverse outcome than men. This was related to factors more common in female patients (advanced age and delayed presentation), and showed that an increased awareness is needed to reduce delayed presentation after symptom onset, especially among women.**

Key Words. **ST-segment elevation myocardial infarction, reperfusion therapy, gender**

Introduction

Overwhelming evidence supports the use of reperfusion therapy, either with thrombolytic drugs or percutaneous coronary intervention, in patients with ST-segment elevation myocardial infarction (STEMI) who are admitted to hospital within 12 hours of symptom onset [1,2]. Nevertheless, many patients with STEMI do not receive reperfusion therapy [3,4].

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Address for correspondence: Marc Cohen, Cardiac Catheterization Laboratory, Newark Beth Israel Center, 201 Lyons Avenue, Newark, NJ 07112, USA. Tel.: 973-926-7852; Fax.: 973-282-0839; E-mail: marcohen@sbhcs.com

Reasons for withholding therapy include presentation after the 12-hour therapeutic window, advanced age, gender, and geographic variations in management practices [3–6]. The Treatment with Enoxaparin and Tirofiban in Acute Myocardial Infarction (TETAMI) randomized trial evaluated different antithrombotic regimens in STEMI patients who were not eligible for reperfusion therapy, thus presenting a unique opportunity to analyze non-reperfused patients [7,8]. The TETAMI registry included the STEMI patients admitted to the same institutions who received reperfusion therapy, as well as those who neither received reperfusion therapy nor were enrolled in the randomized trial [9]. The aim of the present analysis was to analyze data from the TETAMI study (trial and registry) to determine if, and why, women are less likely to receive reperfusion therapy and to compare outcomes after STEMI in women with those in men.

Methods

Patient selection

The design and methods of the TETAMI randomized trial have been described previously in detail [7,8]. Briefly, patients had to be 18 years of age or older with acute STEMI. For inclusion, all patients were required to have ischemic symptoms of at least 30 minutes duration within the previous 24 hours, accompanied by sustained ST-segment elevation of >0.2 mV in at least 2 precordial leads, or of >0.1 mV in limb leads, or new left-bundle-branch block or new *Q* wave plus elevated levels of creatinine kinase-MB, creatinine kinase, or serum troponin. Exclusion criteria included Killip class IV, cardiogenic shock, planned revascularization within 48 hours, contraindications to any of the study drugs, thrombocytopenia, current treatment with anticoagulants or a glycoprotein IIb/IIIa receptor antagonist, renal insufficiency, and lack of informed consent. For the registry, exclusion criteria were: participation in the randomized trial and inability to comply with 30-day and 6-month follow-up. In addition, for these analyses, patients with a Killip class of IV were excluded. All patients gave informed consent. The protocol received ethics committee approval in all countries.

Randomization and treatment

Figure 1 shows the distribution of patients entered into the randomized trial and registry. All eligible patients who were enrolled in the randomized trial were randomized to receive unfractionated heparin or enoxaparin, and tirofiban or placebo in a 2 × 2 factorial design. All patients received a minimum initial dose of 160 mg aspirin, followed by at least 30 days of 100–325 mg aspirin. Patients enrolled in the registry were categorized as either 'received reperfusion therapy' or 'did not receive reperfusion therapy'.

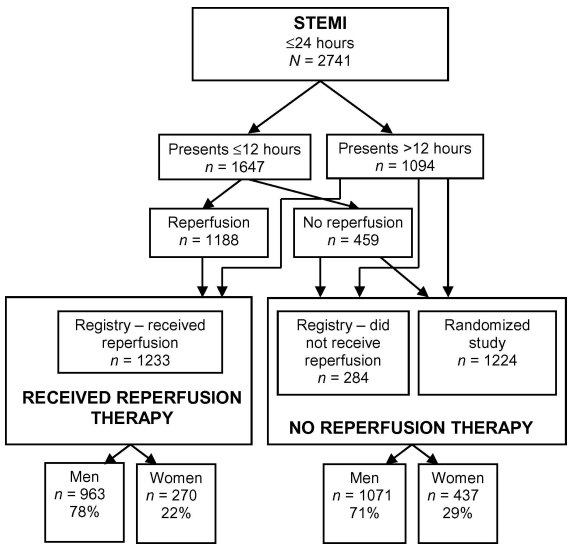

Fig. 1. *Overview of the TETAMI study (randomized trial and registry). STEMI = ST-segment elevation myocardial infarction.*

End points

The primary end point was the combined incidence of all-cause death, reinfarction, and recurrent angina, analyzed at 30 days. Secondary end points included the composite of death and reinfarction at 30 days, incidence of all-cause death at 30 days, recurrent angina at 30 days, and invasive cardiac procedures. Recurrent infarction was diagnosed on the basis of symptoms, changes in electrocardiographic findings and serum cardiac markers, using predefined criteria [7,8]. Recurrent angina was defined as (i) a single episode of angina at rest lasting at least 20 minutes or at least 2 episodes lasting at least 10 minutes within 24 hours, accompanied by new ST-segment changes, or (ii) angina associated with invasive cardiac procedures or rehospitalization for unstable angina. Safety parameters recorded included the incidence of major hemorrhage, which was defined using Thrombolysis In Myocardial Infarction (TIMI) criteria [10].

Statistics

The incidence of the triple end point at 30 days was described for men and women in the following groups: registry—received reperfusion therapy, registry—did not receive reperfusion, and randomized trial. A multivariate analysis was performed to determine predictors of not receiving reperfusion therapy. Predictors of outcomes (30-day composite end point or death) were also analyzed. The following variables were included in the analysis, continuous variables were analyzed in a categorical manner: age (<60, 60–75, >75 years), gender, time from symptom

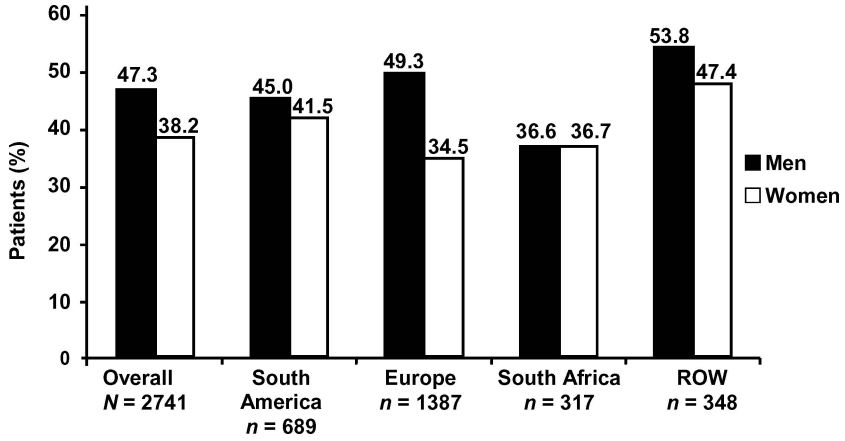

Fig. 2. *Patients receiving reperfusion therapy (thrombolytic therapy or percutaneous coronary intervention), by gender and region. ROW = rest of the world (Australia, New Zealand, USA, and Israel).*

onset to admission (<6 hours, ≥6 hours), systolic blood pressure (≤100, >100), diastolic blood pressure (≤80, >80), heart rate, Killip class I versus II or III, and geographic region (South America; Europe; South Africa; and the rest of the world, which included Australia, New Zealand, USA, and Israel). A backward analysis was performed, with a significance of $p = 0.05$ for removal of variables from the model. Hosmer-Lemeshow statistics for goodness of fit were calculated. Statistical analyses were performed using the Statistical Analysis System (SAS) software package version 8.2.

Results

Baseline characteristics

A total of 2741 patients (2034 men and 707 women) were enrolled in the TETAMI randomized trial and registry (Fig. 1). Baseline characteristics of the patients, by treatment status with reperfusion and gender are shown in Table 1. Compared with treated patients, patients who did not receive reperfusion tended to be older and to present later after symptom onset. Of the total number of patients included in both the randomized trial and registry, a trend towards more men than women receiving reperfusion therapy was observed (47.3 vs. 38.2%). This trend was observed for all geographic regions studied except for South Africa, where there appeared to be no difference between the number of men and women receiving reperfusion therapy (Fig. 2). Female patients tended to be older, have a higher Killip class rating, and present slightly later from symptom onset (Table 1).

A trend towards a lower incidence of the 30-day composite end point of death, reinfarction, and recurrent angina was observed for both reperfused compared with non-reperfused patients (10.9 vs. 17.3%),

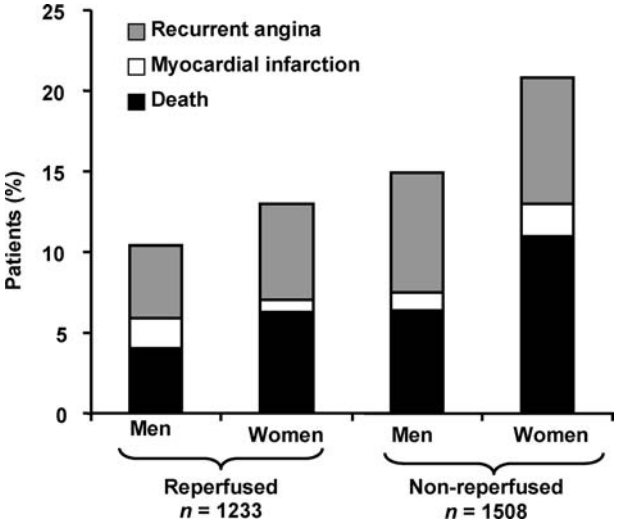

Fig. 3. *Thirty-day composite end point by gender and reperfusion status.*

and for men compared with women (13.3 vs. 17.8%). Overall, men receiving reperfusion appeared to have the best prognosis, and women not referred for reperfusion had the worst prognosis (Fig. 3). This pattern was evident in all geographic regions.

Among all of the factors examined, multivariate analysis identified age >75 years, time from symptom onset to hospital admission, high systolic blood pressure and region (South Africa) as significant independent predictors ($p < 0.05$) of not receiving reperfusion therapy (Table 2). The Hosmer-Lemeshow value for this model was 0.590, with a c-statistic of 0.896. Significant predictors of the triple end point ($p < 0.05$) included not receiving reperfusion, age >60 years, and higher Killip class. Geographic region (Europe) was a predictor of not having

Table 1. *Baseline Characteristics of Patients in the TETAMI Study (Randomized Trial and Registry), by Treatment Status and Gender*

	Registry, received reperfusion ($n = 1233$)		Did not receive reperfusion (randomized trial + registry) ($n = 1508$)	
Characteristic	Men ($n = 963$)	Women ($n = 270$)	Men ($n = 1071$)	Women ($n = 437$)
Median age (years)	58	69	61	71
Killip class I	85.6%	75.6%	86.0%	77.6%
Killip class II	12.8%	21.1%	12.7%	18.8%
Killip class III	1.7%	3.3%	1.3%	3.7%
Median time from symptom onset to admission (hours)	2.5	2.7	16.4	16.7
Median blood pressure (mmHg)	130/80	137/80	130/80	135/80
Heart rate, bpm	76	76	74	78

bpm: beats per minute; TETAMI: Treatment with Enoxaparin and Tirofiban in Acute Myocardial Infarction.

Table 2. *Predictors of Not Receiving Reperfusion Therapy ($N = 2716$; Patients with Missing Data Deleted)*

	Coefficient			Odds ratio	
Variable	Estimate	SE	p value*	Estimate	95% Wald confidence interval
Age 60–75 years	−0.205	0.127	0.1083	0.815	0.635–1.046
Age >75 years†	−0.855	0.179	<0.0001	0.425	0.300–0.604
Systolic blood pressure >100 bpm†	−0.564	0.194	0.0035	0.569	0.389–0.831
Time to treatment ≥6 hours†	−3.922	0.120	<0.0001	0.020	0.016–0.025
Geographic region					
South America	−0.058	0.201	0.7732	0.944	0.636–1.399
Europe	−0.100	0.184	0.5869	0.905	0.631–1.298
South Africa†	−0.778	0.239	0.0011	0.459	0.287–0.734
Female gender	Not retained				
Killip class	Not retained				
Heart rate >80 bpm	Not retained				

*Wald chi-square.

†Significant, $p \leq 0.05$.

bpm: beats per minute; SE: standard error.

Probability modeled: having reperfusion therapy. The Hosmer-Lemeshow value for this model was 0.590, with a c-statistic of 0.896.

a triple end point (Table 3). The Hosmer-Lemeshow value for this model was 0.436, with a c-statistic of 0.660. The significant independent predictors of death at 30 days ($p < 0.05$) were age >60 years, higher Killip class, low systolic blood pressure, heart rate, time from symptom onset to hospital admission, and the geographic regions South America and South Africa (Table 4). The Hosmer-Lemeshow value for this model was 0.131, with a c-statistic of 0.778.

Discussion

The present study, based on prospectively gathered data on all-comers with STEMI within 24 hours of symptom onset, demonstrates important differences in admission characteristics and outcomes between men and women with STEMI. In general, women have a higher mortality rate, whether or not they receive reperfusion therapy, compared with men. These results parallel those of previous studies that also show that women with acute myocardial infarction have a worse prognosis than men [5,11,12], even beyond 1 year [13,14].

Similar findings to ours regarding in-hospital mortality were reported in a prospective registry of 9589 European patients with acute coronary syndromes, although this gender difference was eliminated after adjusting for age and other confounding factors [12]. Data from the North American National Registry of Myocardial Infarctions 2 (NRMI 2) showed that, of the 384 878 patients surviving to reach hospital after an acute myocardial infarction, age was an important

Table 3. *Predictors of Triple End Point (N = 2716; Patients with Missing Data Deleted)*

	Coefficient			Odds ratio*	
Variable	Estimate	SE	*p* value‡	Estimate	95% Wald confidence interval
Reperfusion‡	−0.460	0.117	<0.0001	0.631	0.502–0.794
Age 60–75 years‡	0.352	0.122	0.0039	1.422	1.119–1.806
Age >75 years‡	0.906	0.139	<0.0001	2.473	1.883–3.247
Killip Class‡	0.697	0.132	<0.0001	2.008	1.551–2.600
Geographic region					
South America	−0.039	0.177	0.8270	0.962	0.679–1.362
Europe‡	−0.530	0.167	0.0015	0.589	0.425–0.817
South Africa	−0.167	0.217	0.4417	0.846	0.553–1.295
Time to treatment ≥6 hours	Not retained				
Female gender	Not retained				
Systolic blood pressure >100 bpm	Not retained				
Heart rate >80 bpm	Not retained				

*Odds ratio adjusted from multivariable analysis.

†Wald Chi-Square.

‡Significant, p ≤ 0.05.

bpm: beats per minute; SE: standard error.

Probability modeled: having a component of the triple endpoint. The Hosmer-Lemeshow value for this model was 0.436, with a c-statistic of 0.660.

Table 4. *Predictors of Death at 30 Days (N = 2716; Patients with Missing Data Deleted)*

	Coefficient			Odds ratio*	
Variable	Estimate	SE	*p* value†	Estimate	95% Wald confidence interval
Age 60–75 years‡	0.821	0.215	0.0001	2.274	1.491–3.468
Age > 75 years‡	1.761	0.229	<0.0001	5.819	3,715–9.114
Killip class‡	1.014	0.180	<0.0001	2.757	1.936–3.925
Systolic blood pressure >100 bpm‡	−0.686	0.239	0.004	0.504	0.316–0.803
Time to treatment ≥6 hours‡	0.545	0.176	0.0020	1.725	1.221–2.438
Geographic region					
South America‡	0.690	0.319	0.0307	1.994	1.066–3.728
Europe	0.314	0.305	0.3040	1.368	0.752–2.489
South Africa‡	1.039	0.352	0.0031	2.828	1.419–5.636
Heart rate >80 bpm‡	0.620	0.171	0.0003	1.858	1.328–2.599
Female gender	Not retained				
Reperfusion	Not retained				

*Odds ratio adjusted from multivariable analysis.

†Wald chi-square.

‡Significant, p ≤ 0.05.

bpm: beats per minute; SE: standard error.

Probability modeled: death. The Hosmer-Lemeshow value for this model was 0.131, with a c-statistic of 0.778.

potential factor for excess mortality in women [5]. However in that study, younger rather than older women had higher rates of mortality after a STEMI than men of the same age. These findings have been confirmed in a more recent study of 8277 patients by the same author [14]. In the current analysis, multivariate analysis also revealed that although female patients had worse outcomes, female gender was not a predictor of either death or the triple end point. Age, not receiving reperfusion therapy, and Killip class were predictive of 30-day all-cause death, myocardial infarction, or recurrent angina (composite end point). These results are similar to those obtained by the GUSTO study group, where in a group of 41 021 patients receiving lytic therapy, female gender was predictive of worse outcome, but advanced age was identified as the strongest predictor of adverse outcome [15]. However, female gender was described in this study as being a borderline predictor of adverse outcome.

Evidence exists to suggest that this increased mortality rate in women may be a result of underutilization of reperfusion therapy [16]. In the current study, women were less likely to receive reperfusion therapy than men, and non-use of reperfusion therapy was predictive of the triple end point. However

in this study, the strongest predictors of not receiving reperfusion therapy were advanced age, delayed presentation, high systolic blood pressure and geographic region (South Africa). Previous studies have shown that women are less likely to be considered for reperfusion therapy than men, in some cases even after adjusting for important clinical differences [17–19]. Despite the higher mortality rates in women, fewer women may receive major diagnostic and therapeutic procedures than men [20–22], even though women treated with early aggressive revascularization procedures may have a better long-term outcome than that of men [23].

The underutilization of thrombolytic therapy in women may be partly a result of a longer time from symptom onset to hospital arrival compared with men [5,18,19,24]. Possible reasons for the longer delay may be the age at which women experience a first myocardial infarction, concomitant chronic diseases, atypical presentation of cardiac symptoms, and a reduced perception of risk of myocardial infarction by women themselves and healthcare providers. These factors are compounded by atypical and more transient symptoms at presentation [24].

In our study, we also found that geographic region appeared to be a predictor of adverse outcome. This should be interpreted with caution, as the number of patients per region was not balanced, and the type of center differed from region to region. South Africa was a predictor of both not receiving reperfusion therapy and death at 30 days, which are probably interrelated, whereas the finding that South America was linked to worse outcome could well be due to other confounding baseline factors that are not controlled for in this analysis. A recent report from the TIMI 11b trial conducted in non-ST-segment elevation acute coronary syndromes, showed that when a larger sample size was compared among regions, such geographic regional differences were not apparent [25].

Conclusions

The findings from the present study of more than 2500 consecutive patients with STEMI prospectively followed from the TETAMI trial and registry show important gender differences in outcomes and treatment of STEMI. Female patients tend to have worse outcomes and receive reperfusion therapy less often than male patients. After multivariate analysis, age and delayed presentation, but not gender, were significant predictors of both non-reperfusion and of adverse outcomes. Non-reperfusion was also an independent predictor of the triple end point. Despite the increase in gender-directed studies in recent years, major gaps remain in our understanding of differences in presentation, prognosis, and response to treatment between men and women. Increased awareness of these differences is needed, particularly to reduce the delay in presentation of women with STEMI and to remove any treatment bias that may exist; i.e. reperfusing more eligible female STEMI patients. Further prospective studies are required to determine optimal therapies for patients ineligible for reperfusion.

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